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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/514,513	02/28/2000	Joseph Chappell	07678/011003	8901

32301 7590 02/10/2005

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EXAMINER

KALLIS, RUSSELL

ART UNIT	PAPER NUMBER
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1638

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/514,513

Applicant(s)

CHAPPELL ET AL.

Examiner

Russell Kallis

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 August 2004 and 15 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 3 and 12 is/are allowed.
- 6) ☒ Claim(s) 1,2,4-11 and 13-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 February 2000 and 26 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submissions filed on 8/24/2004 and 11/15/2004 have been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-11, 13-15 remain and new Claims 16-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for the reasons of record set forth in the Official actions mailed 7/30/2003, 3/04/2004 and 6/16/2004. Applicant's arguments filed 8/24/2004 and 11/15/2004 have been considered but are not deemed persuasive.

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Applicant broadly claims plant cells comprising nucleic acid molecules encoding a chimeric isoprenoid synthase having a non-naturally positioned or asymmetrically positioned functional domain that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase and a chimeric isoprenoid synthase comprising a first domain and a second domain from a different isoprenoid synthase.

Applicant describes TEAS and HVS cDNA incorporated through reference (Back and Chappell, J. Biol. Chem. 1995, Vol. 270, pp. 7375); oligonucleotides of SEQ ID NO: 1-6 for constructing chimeric synthases; domain maps of chimeric sesquiterpene synthases CH1-CH14 in Figure 4a comprising sections of TEAS and HVS; altered aristolochene and vetispiradene ratios produced by CH4 and CH10-CH14; Figures 7 and 8 show hypothetical domain switching and hypothetical reaction products for chimeric quiescent-casbene synthase and chimeric quiescent-cadinene synthase.

Applicant does not describe all chimeric isoprenoid synthases having chimeric or asymmetrically positioned homologous domains that synthesizes any one or at least two of any possible kind of isoprenoid or a representative number of chimeric synthases comprising first and second domains from different isoprenoid synthases.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial

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portion of the genus.” See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of chimeric isoprenoid synthases that synthesize reaction products not produced by the non-chimeric isoprenoid synthase. Applicants only describe chimeric sesquiterpene synthases of TEAS and HVS chimeric variants CH4 and CH10-CH14 that demonstrated a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type isoprenoid synthase. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of chimeric isoprenoid synthases. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for chimeric sesquiterpene synthases that demonstrate a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type isoprenoid synthase, it remains unclear what features identify a chimeric isoprenoid synthase that produces the two reaction products not normally produced together by the wild type isoprenoid synthase. Since the genus of chimeric isoprenoid synthases has not been described by specific structural features that demonstrate a reaction product not produced by the non-chimeric isoprenoid synthase, the specification fails to provide an adequate written description to support the breadth of the claims.

Based upon the disclosure of TEAS and HVS, there is insufficient relevant identifying characteristics to allow one skilled in the art to completely determine the structure of chimeric isoprenoid synthases, that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild

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type or non-chimeric isoprenoid synthase, absent further guidance. Since the claimed genus encompasses undisclosed or yet to be discovered sequences that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase, the disclosure TEAS and HVS chimeric variants CH4 and CH10-CH14, does not provide adequate description of the broadly claimed genus. In view of the level of knowledge and skill in the art one skilled in the art would not recognize from Applicant's disclosure that Applicant was in possession of chimeric isoprenoid synthases having a non-naturally/chimeric or asymmetrically positioned functional domain that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase, other than chimeric variants of comprising TEAS and HVS, CH4 and CH10-CH14, as broadly claimed.

Applicant asserts that the written description requirement is satisfied by the insertion of language reciting a conserved amino acid motif, together with language that specifies the relative position of the specific domains of the chimeric synthase (response page 15 lines 10-15). The motif that Applicant has recited is found in both non-chimeric wild type isoprenoid synthases and Applicant's chimeric isoprenoid synthases. Since both chimeric isoprenoid synthases and non-chimeric synthases have the motif it is not a defining element of a chimeric synthase. Further, not all isoprenoid synthases share the same mechanisms, domain requirement for activity, products formed, or relative position of specific domains, and thus Applicant has not described a representative number of chimeric isoprenoid synthases.

Applicant asserts that the chimeric polypeptides are defined by specific structural features that include the domains that control the synthesis of specific isoprenoid products (response page 16 lines 6-8). Applicant has not described chimeric isoprenoid synthases that synthesize a broad range of isoprenoid products or a broad range of specific isoprenoid products. Applicant only describes chimeric isoprenoid synthases CH4 and CH10-CH14 that produced sesquiterpenes 5-epi-aristolochene and vetispiradiene.

Applicant asserts that there is sufficient structural and functional information supported by “other results on domain swapping” about the polynucleotides and the encoded polypeptides to provide a written description of the invention (response page 16 lines 15-22), and that their work establishes that chimeric isoprenoid synthases catalyze a spectrum of reaction products not obtained with naturally occurring wild type synthases (response page 16 lines 23-25). It is not clear what Applicant means by “other results on domain swapping”. Applicant has only described chimeric isoprenoid synthases CH4 and CH10-CH14 that synthesized 5-epi-aristolochene and vetispiradiene in varying ratios when transformed into *E. coli* on page 17 in Table 1, wherein 5-epi-aristolochene and vetispiradiene are the natural products of the respective wild type tobacco and hanbane enzymes domains of which are comprised within the chimera. Applicant has not described chimeras of isoprenoid synthases that synthesize novel isoprenoids.

Applicant further asserts that the published work of Schalk *et al.*, PNAS, 97; (22): pp. 11948-11953 shows that the authors identified the conserved domains and were able to reorganize the conserved domains to produce novel chimeric isoprenoid synthases having altered activities (response page 19 lines 1-8). This is not made evident by Schalk *et al.* (PNAS, 97; (22): pp. 11948-11953), where the author’s remarks are directed towards the involvement of

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specific residues and the importance of progressively placed directed mutations into a conserved region and not asymmetrically positioned domains as being determinant for changes in product formation. Further, the swapping of portions of the two respective enzymes analyzed by Schalk *et al.* did not follow recognized intron exon boundaries but rather were determined as a matter of conveniently located restriction sites within the cDNA. Moreover, the publication date of the cited reference is well after the date of the priority claim (4/12/1996) of the instant application and does not support Applicant's assertion that the reference provides a description of the broadly claimed genus of chimeric isoprenoid synthase polypeptides and polynucleotides encoding said polypeptides.

Applicant asserts that the published work of Erickson H. *et al.* J. Am. Chem. Soc.; 2003 vol. 125, pp. 6886-6888; see page 6886, is not applicable to the issues of chimeras that have the isoprenoid synthase activity that forms either 5-*epi*-aristolochene and vetispiradene (response page 19 lines 15-26). Those remarks were made under lack of enablement and not written description.

Claims 1-2, 4-11, 13-15 remain and new Claims 16-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for plant cells and plants comprising chimeric variants of sesquiterpene cyclases (e.g. TEAS and HVS and CH4, CH10-CH14), does not reasonably provide enablement for plant cells and plants comprising any chimeric isoprenoid synthase having an asymmetrically positioned homologous domain that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase. The specification does not enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

Applicant broadly claims plant cells and plants comprising nucleic acid molecules encoding a chimeric isoprenoid synthase having a non-naturally positioned or asymmetrically positioned functional domain that synthesizes a reaction product not produced by the non-chimeric isoprenoid synthase or at least two reaction products not normally produced together by the wild type or non-chimeric isoprenoid synthase, or plants or plant cells comprising a chimeric isoprenoid synthase comprising a first domain and a second domain from a different isoprenoid synthase.

Applicant teaches TEAS and HVS cDNA incorporated through reference (Back and Chappell, J. Biol. Chem. 1995, Vol. 270, pp. 7375); oligonucleotides of SEQ ID NO: 1-6 for constructing chimeric synthases; domain maps of chimeric sesquiterpene synthases CH1-CH14 in Figure 4a comprising sections of TEAS and HVS; Figure 6 shows the domain switching strategy that produced CH4 and resulted in a synthase having an altered enzyme activity; Figures

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7 and 8 show hypothetical domain switching and hypothetical reaction products for chimeric quiescent-casbene synthase and chimeric quiescent-cadinene synthase; cloning of CH1-CH14 using said oligonucleotides of SEQ ID NO: 1-6 on pages 10-16; altered aristolochene and vetispiradene ratios produced by CH4 and CH10-CH14 when transformed into *E. coli* on page 17 in Table 1; and the structure for potential chimeric quiescent synthases on pages 18-19; and potential chimeric casbene and cadiene synthases on pages 19-20; and prophetic transformation and expression of bacteria, yeast and plants using said chimeric synthases on pages 20-36.

Applicant does not teach all nucleic acid molecules encoding functional or nonfunctional domains of isoprenoid synthases that could be used as asymmetrically positioned homologous domains in chimeric isoprenoid synthases other than the nucleic acid molecules encoding the functional chimeras of CH4 and CH10-CH14 comprising domains from TEAS and HVS that when combined form a chimera synthesizing 5-epi-aristolochene and vetispiradene at various ratios when transformed into *E. coli*.

The state of the art for designing chimeric proteins having modified catalytic function and altered products is highly unpredictable especially when changes are extrapolated onto similar enzymes that do not share the same biochemical mechanism. Without appropriate guidance, one of skill in the art would not know which domains when swapped would be effective. The unpredictability is evident in a newly defined group of monoterpene synthases, a sub group of the claimed isoprenoid synthases, isolated from snapdragon (Dudareva N. et al., *The Plant Cell*, May 2003, Vol. 15, p. 1227-1241; see page 1237 column 2 and page 1238 Figure 10). The isolated polynucleotides did not encode a conserved protein motif that is associated with the biochemical mechanism of the monoterpene synthases identified previously from other

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plant species and were lacking a 200 amino acid region common to the subfamily. Hence there appears to be a different mechanism at work in the monoterpene synthases isolated from snapdragon as compared to other species. Therefore, not all isoprenoid synthases are similar enough to allow for general assumptions in their redesign.

Given the unpredictability in the art as to which domains from which plants would tolerate chimerization; the breadth of the claims encompassing any plant cell comprising any number of enzymatic domains selected from a broad category of isoprenoid synthases; the lack of guidance in the specification or in the prior art as to which domains of the isoprenoid synthase enzyme family would best serve the invention; one would not know based upon Applicant's disclosure which embodiments would be inoperable and predictably eliminated. Thus, undue trial and error experimentation would be needed to make and clone a multitude of non-exemplified isoprenoid synthase chimeras and to test them in a myriad of non-exemplified expression systems for a multitude of altered isoprenoid products. Therefore, the invention is not enabled for the scope set forth in the claims.

Applicant asserts that the Examiner recited Schalk & Croteau (2000) and El Tamer (2003) as lack of enablement that there is a not a reasonable probability of producing of producing active chimeric isoprenoid synthases using domain swapping (response pages 21-22) that the specification may omit detail when the state of the art is high (response page 23 lines 1-8) that the degree of unpredictability is overcome by the skill of those of ordinary skill (response page 24 lines 1-7), that the scope of the claimed invention is relatively restricted such that undue experimentation is not present or it is minimal (response page 25 line 14 to page 26 line 2) and that the state of the art does not suggest unpredictability (response pages 26-27).

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The published work of Schalk *et al.*, PNAS, 97; (22): pp. 11948-11953 shows that the authors identified the conserved domains and were able to reorganize the conserved domains to produce novel chimeric isoprenoid synthases having altered activities (response page 19 lines 1-8). This is not made evident by Schalk *et al.* (PNAS, 97; (22): pp. 11948-11953), where the author's remarks are directed towards the involvement of specific residues and the importance of progressively placed directed mutations into a conserved region and not asymmetrically positioned domains as being determinant for changes in product formation. Further, the swapping of portions of the two respective enzymes analyzed by Schalk *et al.* did not follow recognized intron exon boundaries, as in the instant application, but rather were determined as a matter of conveniently located restriction sites within the cDNA. Moreover, the publication dates of the cited references 2000 and 2003 are well after the date of the priority claim (4/12/1996) of the instant application and do not support Applicant's assertions that the references provide enablement by reflecting the state of the art for making and using the broadly claimed genus of chimeric isoprenoid synthase polypeptides or provide evidence that the degree of unpredictability is overcome by one of ordinary skill. Applicant's remarks that undue experimentation is not present or that it is at least minimal, because the scope of the claims is limited, is not well founded. The enablement art cited Dudareva N. et al., The Plant Cell, May 2003, Vol. 15, p. 1227-1241 clearly shows that not all isoprenoid synthases are similar enough to allow for general assumptions in their redesign and thus the degree of extrapolation introduces a significant amount of unpredictability. Furthermore, see *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970) which teaches "That paragraph (35 USC 112, first) requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to

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persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.”

Claims 3 and 12 are allowed.

Claims 1-2, 4-11, 13-15 and 16-29 are rejected.

The claims are deemed free of the prior art given the failure of the prior art to teach or reasonably suggest a chimeric isoprenoid synthase encoding polynucleotides comprising the coding regions of the active domains and ratio forming domain of TEAS from Tobacco and HVS from henbane and plant cells and plants transformed therewith.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink that reads "Russell Kallis". The signature is written in a cursive, flowing style.

Russell Kallis Ph.D.
February 4, 2005